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EDITORIAL COMMENT

Myocardial Effects of PDE5 Inhibition

More Function With Less Mass*

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Before the 1980s, cardiac hypertrophy was thought to be a compensatory response of the heart to hemodynamic overload that normalized left ventricular (LV) wall stress and permitted individual cardiac myocytes to operate under a normal load. However, during the last 3 decades, we have increasingly recognized that the cellular remodeling that occurs during compensatory hypertrophy, including altered gene expression, can be deleterious and can contribute to the progression to heart failure. Prominent among the changes in gene expression in the hypertrophic response to pressure overload are those responsible for intracellular calcium homeostasis. This includes decreased levels of the sarcoplasmic reticulum Ca^{++} adenosine triphosphatase, the protein responsible for removal during diastole of 75% of the calcium present in the cardiomyocyte cytoplasm. Furthermore, clinical investigations have supported the contention that cardiac hypertrophy that occurs to compensate for pressure overload, such as is seen in essential hypertension, is adversely prognostic (1,2).

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More recently, investigations of the response of animal models using transgenic mice undergoing hemodynamic stress have allowed us to begin to understand that the intracellular signaling that initiates the compensatory hypertrophic response can also be responsible for the progression to heart failure. These studies have shown that the calcium-sensitive phosphatase calcineurin and its activation of the nuclear factor of activated T cells is a critical signaling pathway for pathologic cardiac hypertrophy (3,4). Transgenic mice deficient in calcineurin activity are resistant to many of the hypertrophic stimuli that we recognize as also leading to heart failure, such as pressure overload and neurohormonal stimulation (5).

Animal models, such as the thoracic aortic constriction (TAC) model used by Nagayama et al. (6) in this issue of the *Journal*, can provide important insights into both the physiology by which hypertrophy leads to heart failure, and the signaling pathways that are altered during this transition. Myocardial signaling through the guanylate cyclase–cyclic guanosine monophosphate pathway has been shown to inhibit gene expression associated with the development of hypertrophy as a result of either adrenergic stimulation or pressure overload (7). This raised the possibility that the enzyme type 5 phosphodiesterase (PDE5), which hydrolyzes the intracellular second messenger cyclic guanosine monophosphate, could inhibit the development of hypertrophy. The PDE5 inhibitor sildenafil, which is used clinically for the treatment of either erectile dysfunction or pulmonary arterial hypertension, was shown to prevent or improve the development of hypertrophy in TAC mice when initiated at the time or early after the thoracic constrictor was placed (8). Deterioration in contractile dysfunction was also prevented by PDE5 inhibition.

Of course, in treating human disease, we usually do not have the opportunity to intervene at the time that a pathological stress begins. Rather, patients are usually seen after the symptoms and signs of disease have already become established. Therefore, in the current study, Nagayama et al. (6) used mice in which hypertrophy, dilation, and systolic dysfunction had been established after 3 weeks of TAC. Natriuretic peptide gene expression was increased, a marker for the adverse cardiac remodeling that was occurring. Sildenafil treatment halted the progression of LV dilation and systolic dysfunction that was seen in untreated animals, and natriuretic peptide gene expression did not increase further, despite the fact that TAC remained. The increase in calcineurin protein expression and regulator gene activity observed as a result of TAC did not progress in mice treated with sildenafil. It is intriguing that translocation of protein kinase C-α, an important step in the regulation of enzymatic sarcolemmal calcium reuptake, was altered by sildenafil treatment in a manner that may be expected to improve diastolic cardiac relaxation.

From the perspective of the clinician, the study by Nagayama et al. (6) represents hope that pharmacological intervention in an animal model of adverse hypertrophy may be translatable to the treatment of human heart failure in the foreseeable future. Previous efforts to reverse the adverse functional consequences of cardiac hypertrophy with β-adrenergic receptor antagonists and inhibitors of the renin-angiotensin-aldosterone system have been disappointing, particularly when initiated in patients with established disease. In this study, not only were the adverse functional consequences of established cardiac hypertrophy reversed by PDE5 inhibition, but also the gene expression that is thought to lead to adverse cardiac remodeling was inhibited. The clinical implications of these findings are being explored in the National Heart, Lung, and Blood

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Institute Heart Failure Network, where patients with heart failure and a normal LV ejection fraction are being randomized to chronic sildenafil therapy or placebo, and indexes of functional capacity and myocardial remodeling are being assessed. The findings of investigations such as the current study by Nagayama et al. (6) encourage the design of clinical investigations and of the innovative use of agents that were initially thought to have very different effects.

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